Current trends in dual antiplatelet therapy: a 2017 update

Biasco, Luigi ; Montrasio, Giulia ; Moccetti, Marco ; Pedrazzini, Giovanni

Abstract: Platelet inhibition represents the cornerstone of cardiovascular therapy, owing to the central role of platelets in the genesis of acute ischaemic events. The aim of this article is to review current evidence and trends in coronary dual antiplatelet therapy (DAPT), such as preloading in patients with an acute coronary syndrome, optimal duration of DAPT after stent implantation and indications for long-term treatment, to provide an overview on the role of DAPT following percutaneous valve and structural interventions, and an update on the most recent information concerning the concomitant use of DAPT and oral anticoagulation. A short glance into future perspectives and trends in DAPT will be given.

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Open issues on DAPT: preloading, optimal length of treatment, the role of extended DAPT

Current trends in dual antiplatelet therapy: a 2017 update

Luigi Biasco, Giulia Montrasio, Marco Moccetti, Giovanni Pedrazzini

Fondazione Cardiocentro Ticino, Division of Cardiology, Lugano, Switzerland

Summary

Platelet inhibition represents the cornerstone of cardiovascular therapy, owing to the central role of platelets in the genesis of acute ischaemic events. The aim of this article is to review current evidence and trends in coronary dual antiplatelet therapy (DAPT), such as preloading in patients with an acute coronary syndrome, optimal duration of DAPT after stent implantation and indications for long-term treatment, to provide an overview on the role of DAPT following percutaneous valve and structural interventions, and an update on the most recent information concerning the concomitant use of DAPT and oral anticoagulation. A short glance into future perspectives and trends in DAPT will be given.

Key words: dual antiplatelet therapy; pretreatment; clopidogrel; prasugrel; ticagrelor

Introduction

Platelet inhibition represents the cornerstone of cardiovascular therapy, owing to the central role of platelets in the genesis of acute ischaemic events. Dual antiplatelet therapy (DAPT) addresses two main pathways of platelet activation: inhibition of cyclo-oxygenase-mediated thromboxane A2 formation by aspirin; and inhibition of the ADP-activated surface receptor $P2Y_{12}$ by means of a family of drugs including cangrelor, clopidogrel, prasugrel, ticagrelor and ticlopidine (fig. 1).

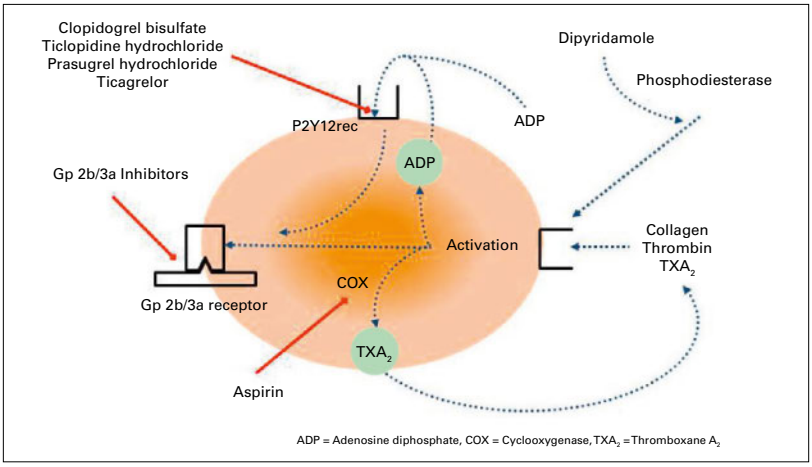


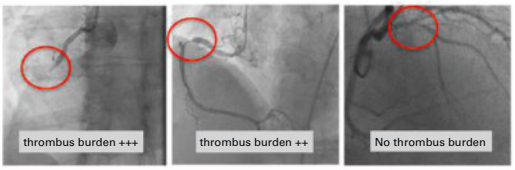
Figure 1: Pathways of platelet activation and their pharmacological targets.

Even though much is known about the efficacy and safety of DAPT, as reflected by the most recent international guidelines [1–3], some specific issues are a matter of ongoing discussion. The aim of this review is to give a concise overview of current knowledge on this topic and to discuss some open issues, such as preloading in patients with an acute coronary syndrome (ACS), which aims to prepare the lesion in view of the imminent percutaneous treatment, the optimal duration of DAPT after stent implantation, defined at the shortest period necessary to protect the stent against the risk of early and late stent thrombosis, and, finally, the long-term treatment (more than 12 months) recently considered as a potential alternative in patients at very high ischaemic risk (fig. 2). A final glimpse of new concepts, upcoming studies and applications of DAPT after valve and structural interventions, as well as in combination with oral anticoagulation, will also be provided.

Historical background

The hypothesis of an auxiliary effect of clopidogrel on top of aspirin in reducing cardiovascular ischaemic events rose from the well-established knowledge that platelet adhesion and activation occur through many different molecular mechanisms [4, 5]. After the introduction of bare metal stents (BMSs) in the early 1990s, aspirin was combined with an additional antithrombotic drug, initially ticlopidine, later clopidogrel, to prevent stent thrombosis during the first 4 weeks after stent implantation [6].

The first data in the BMS era, showing a clinical advantage of extended (>1 month) combination therapy with clopidogrel and aspirin in non ST-segment elevation ACS, came in 2001 from the CURE trial (Clopidogrel in Unstable Angina to prevent Recurrent Events), where the prolonged combined treatment led to an absolute reduction of 2.1% in risk for the composite endpoint, with a benefit maintained over time, particularly in the subgroup of patients undergoing percutaneous revascularisation [7, 8]. A similar trend was observed in 2003 in the CREDO trial, which showed an absolute 3% and a relative 27% risk reduction in the cumulative



Clinical condition	STEMI	NSTEMI	Stable CAD
Invasive approach	Emergency PCI (<90 min)	Urgent PCI (24–48 h)	Elective PCI
Goal of DAPT			
• Hours/Minutes before PCI (preloading)	Lesion preparation	Lesion preparation	–
• Months after PCI	Stent Protection (9–12 months)	Stent Protection (9–12 months)	Stent Protection (3–6 months)
• Years after PCI	Patient Protection (in selected cases)	Patient Protection (in selected cases)	Patient Protection (in selected cases)

Figure 2: Current open issues in dual antiplatelet therapy.

endpoint when comparing 1 month with 12 months of DAPT [9].

A few years later (2005–2006), safety issues with first-generation drug eluting stents (DESs), concerning the occurrence of late and very late stent thrombosis related to the use of antiproliferative drugs inhibiting complete re-endothelialisation for a prolonged time, prompted concerns about the optimal length of DAPT [10–13].

The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) was the first to hypothesise that DAPT lasting more than 12 months could provide greater protection against recurrent events than aspirin alone [14].

More recently, two large ground-breaking trials, TRITON-TIMI 38 and PLATO, tested two new $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, and reassessed the antithrombotic approach in patients presenting with ACS [15, 16].

Available drugs

A summary of currently used $P2Y_{12}$ inhibitors is available in table 1.

Clopidogrel

Clopidogrel (300–600 mg loading dose and 75 mg/day maintenance dose) is an oral thienopyridine derivative. Its active metabolite blocks platelet $P2Y_{12}$ receptors irreversibly, thereby preventing the binding of adenosine diphosphate (ADP) and thus counteracting ADP-dependent activation of GpIIb-IIIa, the major platelet receptor for fibrinogen. As an inactive prodrug, clopidogrel requires a two-step oxidation by the hepatic cytochrome P450 system (specifically by CYP2C19) to generate an active metabolite. This two-step conversion results in a slower onset of action than those of prasugrel and ticagrelor. Furthermore, substantial interindividual variability in the antiplatelet response to this drug has been documented: several different alleles of *CYP2C19* have been related to reduced or increased enzymatic activity of the cytochrome and variable clinical efficacy of clopidogrel.

Prasugrel

Prasugrel (60 mg loading dose and 10 mg/day maintenance dose) is an orally inactive prodrug, also derived from thienopyridine, which irreversibly binds and thus inhibits $P2Y_{12}$ receptors on platelets. Prasugrel requires conversion to an active metabolite through a one-step cytochrome P450-dependant reaction, ensuring a faster onset of action and a more predictable clinical effect than with clopidogrel. According to the TRITON-TIMI 38 post-hoc analysis data, prasugrel is contraindicated in patients with prior stroke (or transient ischaemic attack), or in patients older than 75

Table 1: Details of available P2Y12 inhibitors.

	Oral administration			Intravenous administration
	Clopidogrel	Prasugre!	Ticagrelor	Cangrelor
Drug class — antiplatelet mechanism	Thienopyridine $P2Y_{12}$ inhibitor	Thienopyridine $P2Y_{12}$ inhibitor	Cyclopentyltriazolopyrimidine $P2Y_{12}$ inhibitor	ATP analogue — ADP $P2Y_{12}$ inhibitor
Loading/maintenance dose	300–600 mg / 75 mg once daily	60 mg / 10 mg once daily	180 mg / 90 mg twice daily	30 pg/kg bolus / 4 pg/kg/min infusion
Reversibility	Irreversible	Irreversible	Reversible	Reversible
Bio-activation	prodrug, variable cytochrome P450 metabolism	prodrug, predictable cytochrome P450 metabolism	Active drug	Active drug
Onset of action	2–6 hours	30 min.	30 min.	2 min.
Duration of action	3–10 days	7–10 days	3–5 days	1–2 hours
Withdrawal before surgery	5 days	7 days	5 days	1 hour
Cost	740 CHF/year	1135 CHF/year	1354 CHF/year	Hospital administration only

years or with low body weight (<60 kg) [2, 3, 14]. The role of a reduced 5-mg dose of prasugrel in these subsets of patients is currently under investigation.

Ticagrelor

Ticagrelor (180 mg loading dose and 90 mg twice a day maintenance dose) is an oral $P2Y_{12}$ receptor antagonist belonging to the chemical class of cyclopentyltriazolopyrimidines [16]. It acts through a double antiplatelet mechanism, inhibiting both $P2Y_{12}$ receptors and adenosine reuptake via the equilabrative nucleoside transporter 1 (ENT1). Unlike clopidogrel and prasugrel, ticagrelor binds reversibly to the $P2Y_{12}$ receptor, leading to a faster offset of action with more rapid recovery of platelet function (5 days). Furthermore, ticagrelor is an orally active drug requiring no metabolic activation, which provides a much faster onset of action and more reliable inhibition than clopidogrel. Adverse effects, potentially linked to its inhibition of ENT1, include dose-related episodes of dyspnoea and bradycardia. To date, the only head-to-head comparison data between ticagrelor and prasugrel come from the recent, but greatly underpowered, Prague 18 trial, which did not show any difference between the two potent antithrombotic drugs in term of predefined endpoints at 7 and 30 days in 1250 "real world" patients with ST-segment elevation myocardial infaction (STEMI) treated with primary PCI [17].

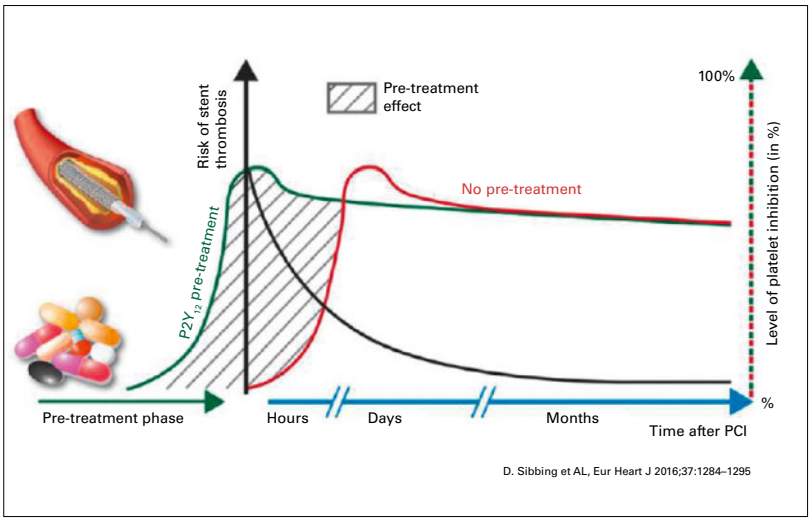


Figure 3: The course of the level of platelet inhibition over time in patients with $P2Y_{12}$ pretreatment (green curve) and in patients without pretreatment (red curve). The opportunity to benefit from pretreatment effect exists within the area with slanted grey lines, the area between the red and green curves. The risk of stent thrombosis (black curve) is highest during and in the early period after percutaneous coronary intervention, with a subsequent decline in risk thereafter. Following a loading dose with $P2Y_{12}$ inhibitors, the maximum level of platelet inhibition is usually seen within hours and up to the day after percutaneous coronary intervention, with a minor decline in inhibition during maintenance therapy before reaching a steady-state level. From: Sibbing D, Kastrati A, Berger PB. Pre-treatment with $P2Y_{12}$ inhibitors in ACS patients: who, when, why, and which agent? Eur Heart J. 2016;37(16):1284–95. Reprinted with permission.

Cangrelor

Cangrelor (30 mg/kg bolus and 4 mg/kg/min infusion) is an intravenous adenosine triphosphate analogue that binds directly and reversibly to the $P2Y_{12}$ receptor, without requiring metabolic activation. It produces reversible and highly effective platelet inhibition, with an almost immediate onset after administration of the intravenous bolus. It has a short plasma half-life (3–6 min), thus allowing restoration of platelet function within 1–2 hours after infusion discontinuation. The CHAMPION-PHOENIX trial, comparing cangrelor with clopidogrel in an all-comers population with stable coronary heart disease and acute coronary syndromes [18], failed to demonstrate any convincing and cost effective advantages of the parenteral drug. Thus, current use of cangrelor is limited to a bridge to surgery in patients with a high bleeding risk, or as an alternative for preloading in ACS patients experiencing nausea and vomiting or reduced oral drug absorption due to impaired peripheral perfusion.

Current role of dual antiplatelet therapy

In the following section we will focus on open issues about DAPT: the role of preloading in acute coronary syndromes, the optimal length of treatment after PCI in stable coronary artery disease and ACS, and the role of extended DAPT after 12 months in selected patients.

Preloading in acute coronary syndromes

The rationale for $P2Y_{12}$ receptor blocker administration before PCI in ACS arises from the observation that the risk of early thrombotic complications, such as re-infarction or acute stent thrombosis, is directly related to the level of platelet reactivity (fig. 3).

Several issues have to be addressed when considering preloading. First, the drug should be administered in a timely manner, early enough to allow complete inhibition at the time of PCI. Secondly, the delay between drug administration and its pharmacological action is related not only to the pharmacokinetics of the molecule, but also to some patient-specific clinical conditions (e.g., STEMI vs NSTEMI, low cardiac output syndromes, etc.) that may further delay absorption. Thirdly, the addition of a second antiplatelet agent on top of aspirin obviously increases the haemorrhagic risk, particularly in the subgroup of patients (5–10%) who might benefit from accelerated surgical revascularisation.

Given these premises, preloading with a $P2Y_{12}$ inhibitor has been considered a rationally appealing approach,

particularly in an era where clopidogrel, with its slow onset of action, was the first and the only available $P2Y_{12}$ inhibitor.

ST-segment elevation ACS

ST-segment elevation myocardial infarction (STEMI) is characterised by strong platelet hyper-reactivity and the need to achieve vessel reperfusion within 90 minutes from symptom onset, clearly requiring fast and adequate platelet inhibition. In this context, the synergic action of heparin, aspirin and ADP receptor antagonists aims to reduce thrombotic activity at the site of plaque rupture and to minimise the thrombogenic impact of the percutaneous intervention.

The indications in guidelines have changed considerably over time, because of the introduction of newer drugs and of contrasting evidence on pretreatment in STEMI patients. Initial experience and, consequently, guidelines were strongly in favour of preloading [19, 20], but newer data challenged this concept [21, 22].

In particular, the recent ATLANTIC trial, the only available randomised study comparing out-of-hospital preloading with administration at the time of PCI in STEMI, failed to show any benefit of the upstream pretreatment in terms of coronary reperfusion and outcome at 30 days, nevertheless with a small but significant reduction of definite stent thrombosis up to 30 days [21]. Even though the 2014 European society of Cardiology (ESC) guidelines on coronary revascularisation still recommend preloading in STEMI [2], recent evidence derived from the ATLANTIC trial weakened the concept of preloading in STEMI and will probably lead to future modifications of recommendations.

Non-ST-segment elevation-ACS

In contrast to STEMI, the therapeutic goal of antithrombotic treatment in the setting of non-ST-segment elevation-ACS (NSTEMI) is to stabilise the coronary plaque in view of mechanical revascularisation, which should take place within 24 to 48 hours [3]. Whereas previous guidelines warmly recommended preloading with a $P2Y_{12}$ inhibitor upstream [20], the only trial testing this hypothesis failed to demonstrate any advantage. In fact, the ACCOAST trial, published in 2013, which compared pretreatment with 30 mg of prasugrel (and a further 30 mg dose at the time of PCI) with prasugrel 60 mg given after diagnostic angiography, did not show any benefit in terms of cardiovascular death, recurrent myocardial infarction, stroke, urgent revascularisation and bailout use of GPIIb/IIIa inhibitors at 7 and 30 days. Instead, a significant increase in major bleedings in the pretreated group was observed [22].

Uncertainties about preloading are mirrored in the 2015 edition of the ESC NSTEMI guidelines, which clearly discourage pretreatment with prasugrel, and give no recommendation favouring or discouraging the use of clopidogrel or ticagrelor, clearly highlighting the lack of evidence to support either strategy [3].

A summary of the current recommendation is given in table 2.

Optimal length of DAPT after stent implantation

Current guidelines recommend routine use of DAPT for 6 months after DES implantation in stable patients and for 1 year after an ACS [2].

Several trials evaluated the hypothesis that a shorter duration of DAPT would guarantee good efficacy and safety after newer-generation stent implantation [23-27], and tested various regimens of DAPT differing in terms of drugs used or length of treatment. Pooled data from these trials, including more than 30 000 patients, concluded that a short course of antithrombotic treatment lasting 3–6 months provides a similar safety profile to longer treatment (12 months) (table 3) [28].

Regardless of different therapeutic options and guideline recommendations, the current trend is to shorten DAPT to the minimum period required according to patient and stent characteristics. So far, this approach has

Table 2: Current recommendations on pretreatment in STEMI and NSTEMI patients. Modified from: Sibbing D, Kastrati A, Berger PB. Pre-treatment with $P2Y_{12}$ inhibitors in ACS patients: who, when, why, and which agent? Eur Heart J. 2016;37(16):1284–95. Reprinted with permission.

STEMI
Routine pre-hospital pretreatment cannot be recommended for patients with STEMI over the in-lab administration of the drug since the two strategies had similar outcomes.
It can be advisable to administer potent and rapidly acting antiplatelet agents (prasugrel or ticagrelor) in the emergency department (i.e., ambulance) **once the diagnosis of STEMI is confirmed and the patient proceeds to primary PCI.**
NSTEMI
It is advisable to administer a potent and rapidly acting antiplatelet agent (prasugrel or ticagrelor) **once the coronary anatomy is known** (and the patient proceeds to immediate PCI).
If prasugrel or ticagrelor are contraindicated, pretreatment with clopidogrel before coronary angiography may be advisable for patients with low bleeding risk and a high likelihood for immediate PCI, especially if radial access is planned.

Table 3: Adverse events according to the length of treatment.

	DAPT 3–6 months	DAPT 12 months	RR
ST* rate (%)	0.5	0.4	0.1
Pooled MI+ (%)	1.7	1.5	0.2
Major bleeding (%)	0.4	0.8	0.4
Death rate (%)	1.7	1.9	0.2

*ST: stent thrombosis; +MI: Myocardial infarction;
Pooled data derived from ISAR SAFE, ITALIC, SECURITY, OPTIMIZE, PRODIGY, RESET and EXCELLENT trials. Modified from G. Montalescot et al. J Am Coll Cardiol. 2015;66:832–47

been evaluated in the RESET [25] and OPTIMIZE (26) trials, which compared 3 and 12 months DAPT after implantation of a zotarolimus-eluting stent in patients with stable coronary artery disease. Both studies demonstrated noninferiority of the shorter treatment for the composite endpoint of all-cause death, myocardial infarction, stroke or major bleeding [26], as well as stent thrombosis and target vessel revascularisation [25].

In patients at high bleeding risk, the predefined DAPT period can be further shortened to 4 weeks when polymer-free drug-eluting stents are used. This is supported by evidence derived from the recent LEADERS FREE trial, which showed similar safety and superior efficacy with these stents as compared with conventional BMSs [29].

Factors that need to be considered in estimating bleeding (favouring shorter DAPT) and ischaemic risk (favouring longer DAPT) are listed in table 4.

DAPT beyond 12 months

Several studies [14, 24, 30–34] hypothesised that prolonged platelet inhibition might result in a better protection against recurrent cardiovascular events.

Table 4: Characteristics related to increased ischaemic/bleeding risk.

Increased ischaemic risk or risk of stent thrombosis (may favour longer-duration DAPT)
Recurrent ischaemic episode on DAPT
ACS presentation in young patients
LV dysfunction
High vascular burden
Chronic stable kidney disease
Additional stent factors
First-generation DES
Stent undersizing
Bifurcation stent
Stent-in-stent
Increased bleeding risk (may favor shorter-duration DAPT)
Very old patients
Short life expectancy
Poor DAPT adherence
End-stage renal failure
Malignancy
Short term candidates for high risk surgery
Severe anaemia
History of prior bleeding
Major haematological disorders
Oral anticoagulation
Low body weight

*Modified from Levine GL et al ACC/AHAGuidelines Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease

The first study evaluating this strategy, the CHARISMA trial (with more than 15 000 patients at risk of, or with established, cardiovascular diseases randomised to either aspirin alone or a combination of aspirin plus clopidogrel for a median of 28 months) failed to demonstrate any advantage of prolonged DAPT but raised some safety concerns in terms of bleeding [14]. A few years later, the DES-LATE study also failed to show any benefit associated with clopidogrel plus aspirin vs of aspirin alone in reducing the incidence of myocardial infarction or death from cardiac causes at 12 months [32].

More recently, the large Dual Antiplatelet Therapy (DAPT) study, compared the extension of DAPT up to 30 months after PCI vs the conventional approach in almost 10 000 event-free patients (30). Prolonged treatment after PCI significantly reduced the rates of stent thrombosis, myocardial infarction and major adverse cardiovascular events. Notably, the reduction in myocardial infarction was significant in both target and non-target lesions, suggesting a secondary prevention effect of long-term DAPT. However, in line with previous studies, a safety concern was raised owing to the increase in moderate to severe bleeding, all-cause mortality and deaths for non-cardiovascular causes in the treatment group.

Finally, the recent PEGASUS-TIMI 54 study, evaluating two different doses of ticagrelor (90 or 60 mg twice daily) plus aspirin vs aspirin alone in more than 21 000 stable high-risk patients (myocardial infarction 1–3 years earlier) with a median follow-up to 33 months, was reported [33]. Consistently with the previous observations, the study demonstrated a significant reduction in terms of the primary efficacy endpoint (combined death, reinfarction, stroke after 3 years). However, an increased risk of major bleeding for the two ticagrelor doses was also observed (2.6% for ticagrelor 90 mg vs 2.3% for ticagrelor 60 mg vs 1.0% for aspirin alone).

A summary of current evidence is available from an elegant meta-analysis, published in 2015 [35], which clearly showed that DAPT maintained well beyond 12 months (up to 24–30 months) reduces the incidence of thrombotic complications, in particular stent thrombosis and myocardial infarction, at the price of an increase in major bleeding and possibly in all-cause mortality. In other words, the dichotomy between efficacy and safety still represents the Achille's heel of this appealing, but challenging approach.

In conclusion, although 2014 ESC guidelines on myocardial revascularisation do not recommend routine extension of DAPT, on the other hand and in the light of the more recent results of the DAPT and Pegasus tri-

als, treatment for more than 12 months can be considered in selected patients with a very high ischaemic burden (e.g., severe coronary artery disease in young patients with multiple risk factors, recurrent events) and at a very low bleeding risk

DAPT and oral anticoagulation

Almost 6–8% of patients undergoing PCI have an indication for chronic oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or new oral anticoagulants (NOACs), as a result of various conditions such as atrial fibrillation, mechanical heart valves and recent or recurrent venous thromboembolism. However, adding antiplatelet agents to warfarin increases non-fatal and fatal bleeding risk more than 3-fold as compared with DAPT [36]. Therefore, clinical judgment and regular reassessment of the indication for OAC is essential.

Current guideline recommendations, derived from large registries [36], from rather small and underpowered randomised trials [37, 38] and from post-hoc analyses of the large randomised trials on atrial fibrillation, still recommend a pragmatic approach mainly based on a clear distinction between stable and acute coronary syndromes and on balancing the systemic bleeding risk by use of validated risk scores [3]. In patients with an acute coronary event and low bleeding risk (HAS-BLED score ≤2) extension of the triple therapy, consisting of aspirin, clopidogrel and either a vitamin K antagonist or NOAC, up to 6 months is recommended. In patients with stable coronary artery disease but at a high haemorrhagic risk (HAS-BLED score >2), a shortened triple therapy (1–3 months) and then a switch to a combination of one antiplatelet drug (either aspirin or clopidogrel) and one oral anticoagulant for up to 12 months is advised.

In accordance with a joint consensus document [39], and in line with the most recent European Guidelines on atrial fibrillation [40], discontinuation of any antiplatelet agent at 1 year is encouraged irrespective of stent type, whereas dual therapy with oral anticoagulation and one antiplatelet agent (aspirin or clopidogrel) may be considered in very selected patients at high risk of recurrent ischaemic events. Prasugrel or ticagrelor as part of triple therapy should be avoided, since these potent $P2Y_{12}$ receptor inhibitors generate an unpredictable risk of fatal bleeding. In addition, when VKAs are used, the prothrombin time international normalised ratio (INR) should be carefully maintained within a target of 2.0–2.5. In patients treated with NOACs, the lowest tested dose for stroke prevention should be applied (e.g., rivaroxaban 15 mg once daily).

The appropriate role of NOACs was investigated in the hypothesis-generating PIONEER AF-PCI [42], which enrolled 2124 patients with non-valvular atrial fibrillation who had undergone PCI. Patients were randomly assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6 or 12 months, or standard therapy with a dose-adjusted VKA (once daily) plus DAPT for 1, 6 or 12 months. Despite its complexity, the study showed a clear benefit in terms of bleeding rates and similar safety for the two rivaroxaban groups as compared with the standard treatment. Even though the trial was not powered to evaluate efficacy, it definitely opens new perspectives in this increasingly important area of antithrombotic treatment.

Open questions and future perspectives

One of the future directions being currently investigated is the potential role of a single antiplatelet treatment with one of the novel potent antithrombotic drugs as an alternative to the conventional DAPT approach.

The ongoing Global LEADERS trial, with more than 16 000 patients included and a 2-year follow up, aims to evaluate whether, after an initial short (1-month) DAPT period, ticagrelor monotherapy will provide similar antithrombotic efficacy without increasing the long-term risk of bleeding [43]. If this trial succeeds in demonstrating this, it could have a revolutionary impact on the clinical management of patients with ischaemic heart disease.

Moreover, the currently ongoing, large-scale COMPASS trial, which includes more than 20 000 patients with documented atherosclerosis, is currently investigating the role of a low dose factor X inhibitor (rivaroxaban 2.5 mg twide daily + aspirin vs rivaroxaban 5 mg twice daily alone vs aspirin alone) in protecting against future cardiovascular events. Also in this case, if efficacy were proven, this would represent an important game-changer in the immediate future [44].

In other words, the antithrombotic perspective could considerably change in the coming years, according to the results of ongoing trials.

Platelet inhibition following structural interventions

The rationale behind platelet inhibition following structural interventions such as transcatheter aortic valve implantation (TAVI), transcatheter edge-to-edge mitral valve repair, left atrial appendage occlusion or patent foramen ovale / atrial septal defect occlusion is

represented by both the need to prevent early thrombosis due to the loss of integrity of the endothelium at the time of the procedure and the need to prevent device thrombosis until complete endothelialisation is achieved.

Although there is a general consensus among cardiologists on the need for platelet inhibition, multiple empirical approaches are adopted in clinical practice. In the absence of clinical trials evaluating alternate antithrombotic regimens, especially after TAVI, no consensus on the optimal agent(s) or duration of therapy is yet available [45].

The recent WRITTEN survey highlighted that DAPT was the most common antithrombotic treatment prescribed at hospital discharge after TAVI. Nonetheless, significant differences were observed in terms of duration, this varying from 1 month in 14.3%, 3 months in 43.8%, 6 months in 35.5%, 12 months in 4.6% and indefinitely in 0.5% centres, while only a minority reported systematic use of single antiplatelet therapy with aspirin alone [46]. Even though some authors [47, 48] questioned the need for DAPT, we strongly support the current recommendation to consider DAPT for a minimum period of 1 to 3 months, as long as data from a large randomised trial are not available.

The concomitant presence of atrial fibrillation or alternative indications for oral anticoagulation clearly add complexity to complexity, and in fact it is not yet clear whether platelet inhibition is needed in the presence of oral anticoagulation.

The introduction of NOACs also opened new possibilities in patients undergoing TAVI. The currently running phase III GALILEO study, in which approximately 1 500 TAVI patients with no previous indication for OAC were randomly allocated to either rivaroxaban 10 mg plus aspirin once daily for 3 months followed by rivaroxaban 10 mg alone, or to standard DAPT with clopidogrel on top of aspirin for 3 months followed by aspirin alone, will most probably add new information and most probably impact on the current practice [49]. Concerning use and length of the dual antiplatelet therapy in the clinical context of structural interventions such as patent foramen ovale, atrial septal defect and left atrial appendage closure or after percutaneous mitral valve repair, the medical evidence is even more scanty and the current practice is still based on empirical recommendations which suggest combining aspirin with clopidogrel for up to 3 months followed by aspirin (or clopidogrel) alone for up to 6 months or as long as required by the clinical condition.

Conclusions

Dual antiplatelet treatment in the clinical context of coronary stent implantation is an evolving area with rapidly changing medical evidence and recommendations. On the basis of recent negative trials, preloading in ACS has been definitely called into question; concerning post-stent DAPT therapy, the current trend is to shorten treatment to the minimum required period and to stratify the approach according to patient and stent characteristics; finally, long term treatment for more than 12 months should only be considered in highly selected cases with a high ischaemic burden and a predicted low bleeding risk.

Ongoing large trials are currently investigating the role of single antiplatelet therapy with the new $P2Y_{12}$ inhibitors and the potential use of new oral anticoagulants both in the setting of coronary artery disease and as an adjunctive therapy after structural interventions.

Correspondence:
Giovanni Pedrazzini, MD
Fondazione Cardiocentro Ticino
Division of Cardiology.
Via Tesserete 48
CH-6900 Lugano
giovanni.pedrazzini[at]cardiocentro.org

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The full list of references is included in the online version of the article at www.cardiovascmed.ch.